

Therapeutic Class Review
Catechol-O-methyltransferase (COMT) Inhibitors

Overview/Summary

The catechol-*O*-methyltransferase (COMT) inhibitor class is a group of antiparkinsonian agents that is comprised of Comtan[®] (entacapone), and Tasmar[®] (tolcapone). Comtan[®] was approved by the Food and Drug Administration (FDA) in 1999 and Tasmar[®] in 1998. Both of these agents are currently only available as brand name entities.¹⁻³

These medications are indicated as adjunctive agents to levodopa/carbidopa in patients with Parkinson's disease who are experiencing signs and symptoms of end-dose wearing-off.^{1,2} In patients with late Parkinson's disease who have been treated with levodopa therapy for a long period of time, the development of motor fluctuations is a common occurrence. One of the first symptoms to occur in regards to these fluctuations is the wearing-off phenomenon. Wearing-off is defined as a shortened therapeutic benefit of each dose of levodopa with patients experiencing a return of their symptoms before the next dose of medication is due. The agents within the COMT-inhibitor class exert their therapeutic effect, by inhibiting the COMT enzyme and reducing the metabolism of levodopa, extending its plasma half-life and prolonging the action of each levodopa dose, consequently decreasing the amount of off-time a patient experiences.^{4,5}

Although these agents share the same mechanism of action, they have distinctive pharmacokinetic profiles. Tolcapone has been shown to exhibit greater bioavailability, area under the curve, T-max, C-max, and a greater affinity to the COMT enzyme. As a result of these pharmacokinetic differences tolcapone increases the levodopa half-life by approximately 80%, as compared to the 40% increase by entacapone. This also appears to be the reason for their differences in dosing administration. Tolcapone is administered three times daily, while entacapone is given concurrently with every dose of levodopa.⁶

Clinical trials have demonstrated that both COMT inhibitors are efficacious in treating patients with Parkinson's disease who have developed motor fluctuations.⁷⁻¹¹ Although the data appears to show a numerical advantage for tolcapone in increasing on-time and decreasing off-time, this difference is not statistically significant. Additionally tolcapone use may be limited due to the significant risks of hepatic failure that are associated with the medication. This risk of hepatic failure has been associated with three deaths and prompted the FDA to require a black box warning be inserted in the medication's product labeling. Due to this safety concern some guidelines have rendered tolcapone a second line agent behind entacapone in the treatment of Parkinson's disease in patients with motor fluctuations^{4,12-15}

The treatment of Parkinson's disease should be individualized with the goal of maintaining an individual's level of functioning with few or no side effects of therapy. Generally, drug treatment is delayed until the symptoms of Parkinson's disease significantly limit the individual's activities of daily living. Available agents used for Parkinson's disease treatment include dopamine precursor/dopamine decarboxylase inhibitors, COMT inhibitors, monoamine oxidase B (MAO-B) inhibitors and anticholinergics.

The European Federation of Neurological Societies (EFNS) guidelines recommend that the addition of either a COMT-inhibitor or an MAO-B inhibitor is appropriate in patients with motor fluctuations. However, they do not explicitly state which agent should be used initially. The EFNS guidelines found no difference between entacapone and rasagiline. They do however recommend that if a COMT-inhibitor is chosen as adjunctive therapy, entacapone should be selected first. Tolcapone should be limited to the patient population that has failed all other available medications.¹²

The American Academy of Neurology guidelines also refrain from making an overall recommendation for a primary agent. They recommend that for patients with motor fluctuations entacapone or rasagiline can be used to reduce off-time. In regards to tolcapone the guidelines recommend it be used with caution and that it requires monitoring.¹³⁻¹⁴

The National Institute for Clinical Excellence (NICE) guidelines recommend that treatment with COMT inhibitors can be used to reduce motor fluctuations in patients with later Parkinson's disease. They also recommend that tolcapone should only be used after entacapone therapy has failed either due to a lack of efficacy or adverse effects.¹⁵

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Entacapone (Comtan [®])	Catechol-O-methyltransferase (COMT) inhibitor	-
Tolcapone (Tasmar [®])	Catechol-O-methyltransferase (COMT) inhibitor	-

Indications

Table 2. Food and Drug Administration Approved Indications^{1,2}

Generic Name	Indication
Entacapone	Adjunct to levodopa/carbidopa in patients with idiopathic Parkinson's disease who are experiencing signs and symptoms of end-dose wearing-off.
Tolcapone	Adjunct to levodopa/carbidopa in patients with idiopathic Parkinson's disease who are experiencing symptom fluctuations and are not responding satisfactory to or are not appropriate candidates for other adjunctive therapies.

Pharmacokinetics

Table 3. Pharmacokinetics^{1,2,16}

Generic Name	Bioavailability (%)	Metabolism (%)	Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Entacapone	35	Hepatic (99.8)	Urine: 10 Feces: 90	Yes (cis-Isomer)	0.4-0.7 (β-phase) 2.4 (γ-phase)
Tolcapone	65 (food given within 1 hour before and 2 hours after dose decreases bioavailability by 10-20)	Hepatic (99.0)	Urine: 60 Feces: 40	None	2- 3

Clinical Trials

Four randomized, double-blind, placebo-controlled studies evaluated the efficacy and safety of adjunctive entacapone and tolcapone given concurrently with levodopa/decarboxylase inhibitor (DCI) in patients with motor fluctuations, compared to placebo and levodopa/DCI.

In a study by Mizuno et al⁷, the mean time in which symptoms were controlled (on-time) increased by 1.4 hours in the entacapone treatment group and 0.5 hours in the placebo group. This corresponded to a

relative increase of 17% versus baseline in the entacapone treatment group. The time in which Parkinson's symptoms were not controlled (off-time) significantly decreased by 1.1-1.3 hours in the entacapone groups compared to 0.4 hours in the placebo group. In a study Rinne⁸ the mean on-time increased by 1.2 hours more in the entacapone group compared to placebo, which constituted a 13% greater increase. Additionally, the mean "off-time" decreased by 1.3 hours more in the entacapone group than in the placebo group. Adler et al⁹ reported that tolcapone treatment arms increased on-time by 2.1-2.3 hours, and reduced off-time by 2.0-2.5 hours. Baas et al¹⁰ reported that the tolcapone group increased on-time by 20.6% and decreased off-time by 26.2% of the baseline value.

A study by Agid et al¹¹ was a randomized double-blind study that evaluated the safety and efficacy of entacapone and tolcapone both as adjunctive therapy given concurrently with levodopa/DCI. The mean increase in on-time was 1.34 hours in the tolcapone group and 0.65 hours in the entacapone group. The difference between on-time in the two treatment groups was not statistically significant.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Mizuno et al⁷</p> <p>Entacapone 100 mg and levodopa/DCI administered as separate entities</p> <p>vs</p> <p>entacapone 200 mg and levodopa/DCI administered as separate entities</p> <p>vs</p> <p>placebo and levodopa/DCI administered as separate entities</p> <p>Each entacapone dose was administered with every levodopa/DCI dose.</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients with PD who were ≥ 20 years old, who exhibited signs of wearing-off, their off-time being 3 hours or more per day on average</p>	<p>N=341</p> <p>4 week run-in period; 8 week treatment period</p>	<p>Primary: Change in time period when the patients was relatively free of parkinsonian symptoms (on-time) while awake between baseline and the end of the 8 week treatment period</p> <p>Secondary: The proportion of on-time and the change in time period when the patient experienced increase in parkinsonian symptoms (off-time) while awake; change in UPDRS parts I,II,III total scores from baseline to the end of the treatment period, safety</p>	<p>Primary: The mean on-time increased by 1.4 hours for both the entacapone 100 mg ($P<0.05$) and 200 mg ($P<0.05$) treatment group. For the placebo group the increase was 0.5 hours (P value not reported).</p> <p>Secondary: The proportion of on-time was significantly increased by 8.3% in the entacapone 100 mg treatment arm and by 8.1% in the 200 mg arm. Off-time was decreased by 1.3 hours for the entacapone 100 mg group and by 1.1 hours in the 200 mg treatment group. No significant differences were detected between the 100 and 200 mg treatment groups (P value not reported).</p> <p>The UPDRS parts I-III total scores improved -4.9 points ($P=0.52$) in the 100 mg group, -5.9 ($P=0.2$) in the 200 mg group, and -4.0 in the placebo group.</p> <p>In the 100 mg entacapone treatment arm, 72.6% of patients reported at least one adverse effect. This was seen in 86.0% of patients in the entacapone 200 mg arm, and in 69.9% of patients in the placebo group. When comparing adverse events between the 200 mg group and placebo the difference was significant ($P=0.0058$). It was also significant ($P=0.0200$) when compared with the 100 mg group.</p> <p>Thirteen patients withdrew from the placebo group due to adverse events, five in the 100 mg entacapone group, and 14 in the 200 mg entacapone group.</p> <p>Overall 37.2% of patients experienced adverse events in the placebo group, 52.2% in the entacapone 100 mg group, and 72.8% in the entacapone 200 mg group. The difference in adverse events was statistically significant when comparing the 200 mg group to the placebo group ($P<0.0010$) and to the 100 mg group ($P=0.0022$). The most common adverse events reported were dyskinesia, somnolence and urine discoloration.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Rinne et al⁸</p> <p>Entacapone 200 mg and levodopa/DCI administered as separate entities</p> <p>vs</p> <p>placebo and levodopa/DCI administered as separate entities</p> <p>Levodopa/DCI doses ranged from 4 to 10 doses daily with a baseline levodopa dose ranging from 701 mg in the entacapone arm to 705 mg in the placebo arm.</p> <p>Each entacapone dose was administered with every levodopa/DCI dose.</p>	<p>DB, PC, PG, RCT</p> <p>Patients with idiopathic PD, with motor fluctuations of the end-of-dose type (wearing-off phenomenon), Hoehn and Yahr stage between 1.5 to 4.0 and an average on time after each single dose of levodopa less than 4 hours</p>	<p>N=171</p> <p>6 months</p>	<p>Primary: Mean daily time period when the patients was relatively free of parkinsonian symptoms (on-time) as derived from the patients' home diaries</p> <p>Secondary: Mean daily time period when the patient experienced increase in parkinsonian symptoms(off-time), mean duration of the beneficial effect following the patients' first morning levodopa dose as recorded in their home diaries, change in UPDRS subscores for parts I, II and III from baseline to the end of the treatment phase, evaluation of global score by both patient and investigator, change in mean daily levodopa dose from baseline to the end of 6 months, safety</p>	<p>Primary: The mean on-time measured from home diaries increased by 1.2 hours (13%) more in the entacapone group than in the placebo group. The difference between groups was statistically significant ($P<0.001$).</p> <p>Secondary: The mean off-time decreased by 1.3 hours (-22%) more in the entacapone treatment group than in the placebo group. The difference between groups was statistically significant ($P<0.001$).</p> <p>The mean duration of the beneficial effect following the first morning dose of levodopa was 0.24 hours greater in the entacapone group than it was in the placebo group. The difference between groups was statistically significant ($P<0.05$).</p> <p>UPDRS subscores for part II decreased by 1.7 points in the entacapone group and by 0.4 point in the placebo group ($P<0.01$). Part III scores decreased by 3 points in the entacapone group and increased by 4.2 points in the placebo group ($P<0.05$). There was no statistically significant differences between treatment groups for UPDRS subscore part I.</p> <p>The global evaluation was in favor of entacapone when performed by the investigator and the patient, however only the investigators values were statistically significant (no data values or P values reported).</p> <p>The mean daily levodopa dose was reduced by 87 mg in the placebo group and increased by 15 mg in the placebo group. The difference between the groups was significant ($P<0.001$).</p> <p>The most frequent adverse events seen with the entacapone group were nausea (20.0%), diarrhea (20.0%), abdominal pain (10.6%) and urine discoloration (10.6%). Six patients withdrew from the entacapone group due to adverse events. Three due to diarrhea, one due to nausea and leg pain, one due to a feeling of intoxication, and one due to pericarditis.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Adler et al⁹</p> <p>Tolcapone 100 mg TID and levodopa/carbidopa administered as separate entities</p> <p>vs</p> <p>tolcapone 200 mg TID and levodopa/carbidopa administered as separate entities</p> <p>vs</p> <p>placebo and levodopa/carbidopa administered as separate entities</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients with idiopathic PD ≥ 30 years old, with ≥ 2 signs of PD (rigidity, resting tremor, or bradykinesia), and had been treated with levodopa/carbidopa for ≥ 1 year with clinical improvement; required to be taking ≥ 4 doses of levodopa/carbidopa and to show predictable end-of-dose wearing off that could not be eliminated with adjustment of existing medications</p>	<p>N=215</p> <p>6 weeks</p>	<p>Primary: Change from baseline to week 6 in off/on time</p> <p>Secondary: Change from baseline to week 6 in the patients UPDRS subscales II, III and I-III total, change in SIP score from baseline to week 6, IGAs of change for symptom severity, wearing-off phenomenon, and overall efficacy and tolerability, safety</p>	<p>Primary: At week 6 the on-time increased by 0.3 hours in the placebo group, 2.1 hours in the tolcapone 100 mg group, and 2.3 hours in the 200 mg group. The difference between both of the treatment groups and placebo were significant ($P < 0.001$). For reduction in off-time the placebo group reported a -0.3 hour reduction, the 100 mg treatment group reported a -2.0 hour reduction, and the 200 mg group reported a -2.5 hour reduction. The difference between both of the treatment groups and placebo were significant ($P < 0.001$).</p> <p>Secondary: Changes from baseline in UPDRS subscale II was -0.7 in the placebo group, -0.4 in the 100 mg entacapone group, and -0.5 in the 200 mg group. The changes in subscale III scores were -1.2 for the placebo group, -2.3 in the 100 mg group and -2.4 in the 200 mg treatment group. Changes in the total subscale score (parts I-III) were -2.2 in the placebo group, and -2.9 in both the 100 and 200 mg group. None of the reductions from any of the UPDRS subscale scores were significantly different from the placebo group (P value not reported).</p> <p>SIP scores also showed no significant difference between the placebo group and either of the treatment group arms (P value not reported).</p> <p>Investigators judged 72% of patients in the tolcapone 100 mg treatment group and 77% in the 200 mg treatment group as having improved. This value was only 26% in the placebo group, with the difference between treatment and placebo groups being significant ($P < 0.001$).</p> <p>Seven percent of patients in the placebo group, 3% in the 100 mg tolcapone group, and 5% in the 200 mg group withdrew from the study due to adverse events. Adverse events were reported by 74% of patients in the placebo group, 86% in the 100 mg tolcapone treatment group, and 97% in the 200 mg group. Only 14% of all adverse events were labeled severe. The most common adverse event seen was dyskinesia. This was seen in 19% of the placebo group, in 62% of the 100 mg group and in 66% of the 200 mg group. The most common adverse events reported in the tolcapone</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment groups were dyskinesia, nausea, dystonia, anorexia, confusion, hallucinations, and excessive dreaming. No consistent changes in vital signs or laboratory test were associated with the tolcapone groups.
<p>Baas et al¹⁰</p> <p>Tolcapone 100 mg TID and levodopa/carbidopa administered as separate entities</p> <p>vs</p> <p>tolcapone 200 mg TID and levodopa/carbidopa administered as separate entities</p> <p>vs</p> <p>placebo and levodopa/carbidopa administered as separate entities</p> <p>First daily dose of tolcapone taken at same time as levodopa and the remaining 2 doses were taken 6 hours apart thereafter.</p>	<p>DB, MC, PC, RCT</p> <p>Male and female patients ≥ 30 years old with at least 2 of the 3 cardinal features of PD (bradykinesia, resting tremor and rigidity) and who exhibited predictable end of dose motor fluctuations in response to levodopa therapy; must also have been treated with levodopa for ≤ 1 year</p>	<p>N=177</p> <p>3 months</p>	<p>Primary:</p> <p>The change in proportion of the time period in which Parkinson's symptoms are controlled (on-time) and the time period in which symptoms are not controlled (off-time) between baseline and month 3</p> <p>Secondary:</p> <p>Reductions in total daily levodopa dose from baseline to month 3, change between baseline and month 3 in UPDRS scores for parts I, II and III, mean reductions in SIP total scores between baseline and month 3 IGA of the degree of change between pretreatment and post-treatment of the tolcapone group compared with placebo, safety</p>	<p>Primary:</p> <p>Compared to the placebo group the on-time in the 100 mg tolcapone treatment group increased by 21.3%, with a statistically significant difference ($P<0.01$). The off-time decreased by 31.5% with a significant difference between the two groups ($P<0.05$). The 200 mg tolcapone treatment group reported a 20.6% increase in the on-time ($P<0.01$) and a non-significant 26.2% decrease in off-time.</p> <p>Secondary:</p> <p>The reduction in total levodopa dose was 108.9 mg ($P<0.05$) in the 100 mg tolcapone treatment group and 122.0 mg ($P<0.01$) in the 200 mg group. Both these dose reductions were statistically significant when compared to the placebo dose reduction of 28.9 mg.</p> <p>Scores on the UPDRS subscale I and II did not change significantly between baseline and month 3 in each of the three treatment arms. The score for subscale III was reduced by 2.1 in the placebo group, 4.2 in the 100 mg tolcapone group, and 6.5 in the 200 mg group. The difference was only statistically significant between the 200 mg group and placebo ($P<0.01$).</p> <p>Mean reductions in SIP total scores between baseline and month 3 were greater in the tolcapone group than with placebo. Total SIP scores were reduced by 0.9 in the placebo group, 1.9 in the 100 mg tolcapone group and 4.2 in the 200 mg tolcapone group. The difference was only statistically significant between the 200 mg group and placebo ($P<0.05$).</p> <p>The IGA of the overall efficacy of treatment showed that by month 3, 70% of patients had improved in the 100 mg tolcapone group and 78% had improved in the 200 mg group. Both these changes were significant when compared with the 37% improvement seen with the placebo group ($P<0.01$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>The most common adverse events reported in the two tolcapone groups were dyskinesia (37.0-52.5%), nausea (27.0-29.0%), insomnia (20.0-25.0%), orthostatic complaints (20.0-27.0%), muscle cramps (17.0-22.0%), excessive dreaming (8.5-23.0%), diarrhea (15.0-25.0%), somnolence (12.0-20.0%) and vomiting (8.5-12.0%).</p> <p>Of the 177 patients in the study 27 withdrew due to adverse events. From the placebo group 7% withdrew, 23% from the 100 mg tolcapone group, and 15% from the 200 mg group. Diarrhea was cited as the most common reason patients discontinued the study. No patients withdrew from the placebo group due to diarrhea compared to 7% in the tolcapone 100 mg group, and 10% in the 200 mg group.</p> <p>Although dyskinesia was the most reported adverse event it was responsible for only two patients withdrawing from the study, one from each tolcapone group. Hallucinations lead to the withdrawal of two patients in the 100 mg group and one patient in the 200 mg group. Orthostatic hypotension led to the withdrawal of one patient overall. Raised liver transaminases were found in three patients of the tolcapone groups causing the withdrawal of one of the three patients.</p>
<p>Agid et al¹¹</p> <p>Entacapone 200 mg and levodopa/DCI administered as separate entities</p> <p>vs</p> <p>tolcapone 100 mg TID and levodopa/DCI administered as separate entities</p> <p>Each entacapone dose was</p>	<p>AC, DB, MC, RCT</p> <p>Patients had a diagnosis of PD of ≥5 years with significant fluctuation of ≥3 hours/day off time despite best medical therapy including up to 12 daily doses of levodopa and entacapone 200 mg</p>	<p>N=150</p> <p>3 weeks</p> <p>Open optimization phase ≥10 days where levodopa doses optimized for balance between efficacy and tolerability</p>	<p>Primary:</p> <p>Proportion of patients with a mean increase in the time period in which Parkinson's symptoms are controlled (on-time) of ≥1 hour/day at the end of the 3 weeks of treatment</p> <p>Secondary:</p> <p>Proportion of patients showing moderate or marked overall improvement in the</p>	<p>Primary:</p> <p>More patients in the tolcapone treatment group 40 (53%) experienced ≥1 hour/day increase in on-time after 3 weeks of treatment when compared to the entacapone group 32 (43%). The difference between the two groups was not statistically significant ($P=0.19$).</p> <p>Secondary:</p> <p>In the entacapone group 7 (9%) showed marked improvement and 12 (16%) showed a moderate improvement. In the tolcapone group 12 patients (16%) showed marked improvement and 17 (23%) showed a moderated improvement per the IGA. Overall there was a greater tendency of improvement in the tolcapone group with the total number of patients with any improvement equaling 29 and 19 in the entacapone group. The difference was not significant ($P=0.08$).</p> <p>There were 10 (13%) patients with an increase in on time of ≥3 hours/day</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
administered with every levodopa/DCI dose.			IGA at the end of the treatment phase, proportion of patients in each treatment group with an increase in on-time of ≥ 3 hours/day, proportion of patients having an increase in on-time of ≥ 1 hour and a moderate or marked improvement according to the IGA, safety	<p>in the entacapone group and 19 (25%) in the tolcapone group (<i>P</i> value not reported).</p> <p>There were 13 (17%) patients in the entacapone group who experienced an increase in on time of ≥ 1 hour and a moderate or marked improvement according to the IGA. For the tolcapone group the number was 24 (32%) (<i>P</i> value not reported).</p> <p>At least one adverse event was reported in 40 (53%) patients in the entacapone group and 43 (57%) in the tolcapone group. The most frequent adverse event was dyskinesia with 22 (29%) reporting this event and 23 (31%) in the tolcapone group. The tolcapone group had 7 (9%) patients with elevated liver enzymes above the upper limit of normal, and this number was 2 (3%) in the entacapone group.</p>

Study abbreviations: AC=active-controlled, DB=double-blind, DCI=decarboxylase inhibitor, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, TID=three times daily

Miscellaneous abbreviations: IGA=Investigators Global Assessment, PD=Parkinson's disease, SIP=Sickness Impact Profile, UPDRS=Unified Parkinson's Disease Rating Scale

Special Populations**Table 5. Special Populations^{1,2,16}**

Generic Name	Population and Precaution				
	Elderly/Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Entacapone	Safety and efficacy not established in pediatric patients. No dose adjustment necessary for elderly patients.	No dose adjustment necessary.	Use with caution in patients with hepatic impairment.	C	Unknown
Tolcapone	Safety and efficacy not established in pediatric patients. No dose adjustment necessary for elderly patients.	No dose adjustment necessary for mild-moderate impairment. Use caution with severe impairment. No safety information available in patients with $Cl_{cr} < 25$ mL/minute.	No dosage adjustment is needed in patients with moderate non-cirrhotic liver disease. Dosage should be reduced in patients with moderate cirrhotic liver disease. Therapy should not be initiated if patient exhibits active liver disease or two SGPT/ALT or SGOT/AST values greater than the upper limit of normal.	C	Unknown

ALT=alanine aminotransferase, AST=aspartate aminotransferase, SGOT=serum glutamic oxaloacetic transaminase, SGPT=serum glutamic pyruvic transaminase

Adverse Drug Events

The most common adverse events reported with entacapone include dyskinesia, nausea, diarrhea and urine discoloration. For tolcapone the most common adverse events include dyskinesia, sleep disorder, nausea, vomiting and excessive dreaming. The most serious adverse event reported with tolcapone is severe hepatocellular injury, which included fulminant liver failure that resulted in death. As of 2005, this fatal event was reported in 3 cases.

Table 6. Adverse Drug Events (%)^{1,2}

Adverse Event	Entacapone	Tolcapone
Cardiac		
Orthostatic complaints	4.3	17
Syncope	1.2	4-5
Central and Peripheral Nervous System		
Confusion	-	10-11
Dizziness	8	6-13
Dreaming excessive	-	16-21

Adverse Event	Entacapone	Tolcapone
Dyskinesia	25	42-51
Dystonia	-	19-22
Fatigue	6	3-7
Hallucination	4.0	8-10
Headache	-	10-11
Hyperkinesia	10	2-3
Hypokinesia	9	1-3
Sleep disorder	-	24-25
Somnolence	-	14-18
Dermatological		
Sweating increased	-	4-7
Gastrointestinal		
Abdominal pain	8	5-6
Anorexia	-	19-23
Constipation	6	6-8
Diarrhea	10	16-18
Nausea	14	30-35
Vomiting	-	8-10
Xerostomia	-	5-6
Musculoskeletal		
Muscle cramps	-	17-18
Respiratory		
Upper respiratory tract infection	-	5-7
Urinary System		
Urinary tract infection	-	5
Urine discoloration	10	2-7
Other		
Falling	-	4-6

-Event not reported.

Contraindications / Precautions^{1,2,16}

Entacapone and tolcapone are contraindicated in patients with hypersensitivities to either of the two medications or their ingredients. Tolcapone is further contraindicated in patients with liver disease, a history of non-traumatic rhabdomyolysis, hyperpyrexia, confusion that is possibly related to the medication, or in patients that were withdrawn from tolcapone due to evidence of tolcapone induced hepatocellular injury. Therapy with tolcapone should not be initiated in patients with two serum glutamic pyruvic transaminase (SGPT)/alanine aminotransferase (ALT) or serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST) values greater than the upper limit of normal. Tolcapone therapy with 200 mg three times a day has been found to have a higher incidence of liver enzyme elevation. Precautions should be taken when administering entacapone concurrently with nonselective monoamine oxidase inhibitor therapy. Hallucinations have also been associated with catechol-O-methyltransferase (COMT) inhibitor therapy, as have cases of rhabdomyolysis and fibrotic complications such as retroperitoneal fibrosis or pleural effusion. Caution is also required when reducing COMT-inhibitor doses or discontinuing the medication as periodic cases of a symptom complex resembling neuroleptic malignant syndrome have been reported in patients where there was an abrupt dose reduction or cessation of therapy. Withdrawal of either medication should proceed slowly.

Black Box Warning for Tolcapone¹

Increased Risk of Potentially Fatal Acute Fulminant Liver Failure

Because of the risk of potentially fatal, acute fulminant liver failure, Tasmar(tolcapone) should ordinarily be used in patients with Parkinson's disease on l-dopa/carbidopa who are experiencing symptom

Increased Risk of Potentially Fatal Acute Fulminant Liver Failure

fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies.

Because of the risk of liver injury and because Tasmar, when it is effective, provides an observable symptomatic benefit, the patient who fails to show substantial clinical benefit within 3 weeks of initiation of treatment, should be withdrawn from Tasmar.

Tasmar therapy should not be initiated if the patient exhibits clinical evidence of liver disease or two SGPT/ALT or SGOT/AST values greater than the upper limit of normal. Patients with severe dyskinesia or dystonia should be treated with caution.

Patients who develop evidence of hepatocellular injury while on Tasmar and are withdrawn from the drug for any reason may be at increased risk for liver injury if Tasmar is reintroduced. Accordingly, such patients should not ordinarily be considered for retreatment.

Cases of severe hepatocellular injury, including fulminant liver failure resulting in death, have been reported in postmarketing use. As of May 2005, 3 cases of fatal fulminant hepatic failure have been reported from more than 40,000 patient years of worldwide use. This incidence may be 10- to 100-fold higher than the background incidence in the general population. Underreporting of cases may lead to significant underestimation of the increased risk associated with the use of Tasmar. All 3 cases were reported within the first six months of initiation of treatment with Tasmar. Analysis of the laboratory monitoring data in over 3,400 Tasmar treated patients participating in clinical trials indicated that increases in SGPT/ALT or SGOT/AST, when present, generally occurred within the first 6 months of treatment with Tasmar.

A prescriber who elects to use Tasmar in face of the increased risk of liver injury is strongly advised to monitor patients for evidence of emergent liver injury. Patients should be advised of the need for self-monitoring for both the classical signs of liver disease (eg, clay colored stools, jaundice) and the nonspecific ones (eg, fatigue, loss of appetite, lethargy).

Although a program of periodic laboratory monitoring for evidence of hepatocellular injury is recommended, it is not clear that periodic monitoring of liver enzymes will prevent the occurrence of fulminant liver failure. However, it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Accordingly, the following liver monitoring program is recommended.

Before starting treatment with Tasmar, the physician should conduct appropriate tests to exclude the presence of liver disease. In patients determined to be appropriate candidates for treatment with Tasmar, serum glutamic-pyruvic transaminase (SGPT/ALT) and serum glutamic-oxaloacetic transaminase (SGOT/AST) levels should be determined at baseline and periodically (i.e. every 2 to 4 weeks) for the first 6 months of therapy. After the first six months, periodic monitoring is recommended at intervals deemed clinically relevant. Although more frequent monitoring increases the chances of early detection, the precise schedule for monitoring is a matter of clinical judgment. If the dose is increased to 200 mg tid, liver enzyme monitoring should take place before increasing the dose and then be conducted every 2 to 4 weeks for the following 6 months of therapy. After six months, periodic monitoring is recommended at intervals deemed clinically relevant.

Tasmar should be discontinued if SGPT/ALT or SGOT/AST levels exceed 2 times the upper limit of normal or if clinical signs and symptoms suggest the onset of hepatic dysfunction (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, pruritus, and right upper quadrant tenderness).

Drug Interactions**Table 7. Drug Interactions^{1,2,16,17}**

Name	Interacting Medication or Disease	Potential Result
Catechol-O-methyltransferase (COMT) inhibitors (all)	COMT substrates (eg, apomorphine, bitolterol, dobutamine, dopamine, epinephrine, norepinephrine, isoproterenol, isoetharine, and methyl dopa)	COMT inhibitors may decrease the metabolism and may result in increased heart rates, possibly arrhythmias, and excessive changes in blood pressure.
COMT Inhibitors (all)	Monoamine oxidase (MAO) inhibitors	Concurrent use would result in inhibition of the majority of the pathways responsible for normal catecholamine metabolism. Patients should not be treated concomitantly. Selective MAO inhibitors such as selegiline appear to pose limited risk.

Dosage and Administration**Table 8. Dosing and Administration^{1,2,16,18}**

Generic Name	Adult Dose	Pediatric Dose	Availability
Entacapone	<u>Parkinson's disease:</u> Tablet: initial, 200 mg, up to a maximum of 8 times/day, as adjunct to levodopa/carbidopa; maximum, 1,600 mg/day	Safety and efficacy in children have not been established.	Tablet: 200 mg
Tolcapone	<u>Parkinson's disease:</u> Tablet: initial, 100 mg three times a day as an adjunct to levodopa/carbidopa; maximum, 200 mg three times a day	Safety and efficacy in children have not been established.	Tablet: 100 mg 200 mg

Clinical Guidelines

According to the National Institute for Health and Clinical Excellence (NICE) there is no universal first-choice therapy for patients with Parkinson's disease.¹⁵ Levodopa, dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors may all be used in patients with early Parkinson's disease for symptomatic treatment. The MAO-B inhibitors are considered more convenient compared to the other agents due to ease of administration and may be considered in patients who need symptomatic treatment prior to the administration of dopaminergic therapy. Anticholinergics should be limited to younger patients with early Parkinson's disease associated with severe tremor. In elderly patients, early use of levodopa is recommended as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events.

In addition, there is no single agent of choice for late stage Parkinson's disease.¹⁵ Levodopa, dopamine agonists, MAO-B inhibitors and catechol-O-methyl transferase (COMT) inhibitors may all be considered to reduce motor fluctuations in patients with late stage Parkinson's disease. For the symptomatic control of wearing-off in late, complicated Parkinson's disease, several strategies have been recommended. Such strategies include increasing the dosing frequency of levodopa or switching to a controlled-release formulation of the medication. Also adding a COMT-inhibitor, MAO-B inhibitor or dopamine agonist as adjunctive therapy is also recommended. If these strategies fail it is recommended that amantadine or an anticholinergic be considered. For the symptomatic control of dyskinesias in late, complicated Parkinson's disease the addition of amantadine is recommended. Other strategies include reducing the dose size of levodopa or discontinuing or reducing the dose of MAO-B inhibitors or COMT inhibitors, however these strategies increase the risk of worsening off-time.

Table 10. Clinical Guidelines^{4,12-15}

Clinical Guideline	Recommendations
<p>National Institute for Health and Clinical Excellence (NICE): Parkinson's Disease: Diagnosis and Management in Primary and Secondary Care (2006)¹⁵</p>	<ul style="list-style-type: none"> • There is no universal first-choice therapy for patients with Parkinson disease (PD). Clinical and lifestyle characteristics of the patient should be taken into account. • Levodopa may be used in patients with early PD for symptomatic treatment with doses kept as low as possible to reduce the development of motor complications. • Dopamine agonists may be used in patients with early PD for symptomatic treatment. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class maybe used if the patient fails therapy or side effects prevents titration. • Monoamine oxidase-B (MAO-B) inhibitors may be used in patients with early PD for symptomatic treatment. • Beta-blockers may be used for symptomatic treatment of selected people with postural tremor, but are not considered first-line agents. • Amantadine may be used in patients with early PD, but is not considered a first-line agent. • Anticholinergics may be used in young patients with early PD for symptomatic treatment associated with severe tremor. These agents are not considered first-line due to limited efficacy and the propensity to cause neuropsychiatric side effects. • Extended-release levodopa should not be used to delay the onset of motor complications in patients with early PD. • Most patients with PD will develop motor complications over time and will require levodopa therapy. Adjuvant medications have been developed to take concomitantly with levodopa to help reduce the motor complications and improve quality of life associated with late stage PD. • There is no single agent of choice for late stage PD. • Extended-release levodopa may help reduce motor complications in patients with late stage PD, but is not considered a first-line agent. • Dopamine agonists may be used to reduce motor fluctuations in patients with late stage PD. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class maybe used if side effects prevent titration. • MAO-B inhibitors may be used to reduce motor fluctuations in patients with late stage PD. • Catechol-O-methyl transferase (COMT) inhibitors may be used to reduce motor fluctuations in patients with late stage PD. This class of medication is taken concomitantly with levodopa. • Amantadine may be used to reduce dyskinesias in patients with late stage PD. • "Drug holidays" should be avoided because of the risk of developing neuroleptic malignant syndrome.
<p>American Academy of Neurology (AAN) Practice Parameter: Initiation of Treatment for Parkinson's Disease: An Evidence Based Review (2002)¹³</p>	<ul style="list-style-type: none"> • Patients with PD, who require symptomatic treatment, may be started with selegiline prior to the administration of dopaminergic therapy. • Selegiline has mild symptomatic benefits in PD, and no convincing evidence of neuroprotective benefits. • Levodopa, cabergoline, ropinirole and pramipexole are effective in ameliorating motor complications and impairment in the activities of daily living (ADL) in patients with PD who require dopaminergic therapy. Of these agents, levodopa is more effective in treating motor

Clinical Guideline	Recommendations
	<p>complications and ADL disability and is associated with a higher incidence of dyskinesias than dopamine agonists.</p> <ul style="list-style-type: none"> • Levodopa or a dopamine agonist may be initiated in patients with PD who require dopaminergic therapy. • Cabergoline, ropinirole and pramipexole resulted in fewer motor complications (i.e., wearing off, dyskinesias, on-off fluctuations) compared to levodopa. • Treatment with a dopamine agonist was associated with more frequent adverse drug reactions (hallucinations, somnolence and edema in the lower extremities) than levodopa. • When initiating treatment with levodopa in patients with PD, either an immediate-release or sustained-release formulation may be used. In clinical trials, there was no difference in the rate of motor complications between the two formulations.
<p>AAN Practice Parameter: Treatment of Parkinson's Disease with Motor Fluctuations and Dyskinesia (2006)¹⁴</p>	<ul style="list-style-type: none"> • Rasagiline and entacapone demonstrated statistically significant reduction in off time as compared to placebo in clinical trials. It is recommended that these two agents should be offered to reduce off-time. • Pergolide demonstrated some improvement in the reduction in off-time as compared to placebo in clinical trials. However, a large number of patients on pergolide experienced more dyskinesias. Pramipexole demonstrated some reduction in off-time in placebo controlled trials. Ropinirole and tolcapone showed reduction in off-time compared to placebo. It is recommended that pergolide, pramipexole, ropinirole and tolcapone can be considered to reduce off-time. Due to side effects and the strength of the studies, entacapone and rasagiline are preferred over pergolide, pramipexole, ropinirole and tolcapone. • Apomorphine, cabergoline and selegiline were studied in clinical trials that lacked proper enrollment and methods to provide conclusive evidence of reducing off-time. It is recommended that these agents may be considered to reduce off-time. • Bromocriptine and extended-release carbidopa/levodopa do not help to reduce off-time. • Amantadine demonstrated reduction in dyskinesia compared to placebo in clinical trials. It is recommended that amantadine may be considered for patients with PD for reducing dyskinesias. • Deep brain stimulation of the subthalamic nucleus may be considered as a treatment option in PD patients to help improve motor function and to reduce motor fluctuations, dyskinesias and medication usage.
<p>European Journal of Neurology: Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Early (Uncomplicated) Parkinson's Disease (2006)⁴</p>	<ul style="list-style-type: none"> • No adequate clinical trials have been conducted to provide definitive evidence for pharmacological neuroprotection. • In the management of early PD, MAO-B inhibitors have a modest benefit in treating the symptomatic complications of PD compared to levodopa and dopamine agonists. These agents are more convenient due to the ease of administration (i.e., one dose, once daily, no titration). • Amantadine and anticholinergics offer minimal symptom control compared to levodopa. • Anticholinergics are poorly tolerated in the elderly and use should be restricted to younger patients. • Levodopa is the most effective anti-Parkinson's drug for symptomatic relief.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Early use of levodopa in the elderly is recommended as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events. • Pramipexole and ropinirole are effective dopamine agonists as monotherapy in the treatment of early stage PD. • Convincing evidence that older agents in the class are less effective than the newer non-ergot agents is lacking. • Dopamine agonists have a lower risk of developing motor complications than compared to levodopa. These agents do have a greater incidence of adverse effects which include hallucinations, somnolence and edema in the lower extremities. • Younger patients should be started on a dopamine agonist as initial treatment to prolong the use of levodopa and the development of motor complications.
<p>European Journal of Neurology: Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Late (Complicated) Parkinson's Disease (2006)¹²</p>	<p><u>Symptomatic Control of Wearing-off</u></p> <ul style="list-style-type: none"> • Adjusting the levodopa dose by increasing the dosing frequency has been beneficial to control off-time. • Switching from the standard formulation of levodopa to the controlled-release formulation improves wearing-off symptoms. • Adding a COMT-inhibitor or a MAO-B inhibitor is effective in reducing off-time by 1-1.5 hours/day. • Adding a dopamine agonist provides modest benefit. All dopamine agonists are equally effective and efficacious in reducing off-time. Pergolide and other ergot derivatives are reserved for second-line use, due to the adverse effect of valvulopathy. • Addition of amantadine or anticholinergics should be considered in patients with severe off symptoms who fail the recommended strategies listed above. <p><u>Symptomatic Control of Dyskinesias</u></p> <ul style="list-style-type: none"> • Patients may benefit for up to 8 months by adding amantadine 200-400 mg/day for the treatment of dyskinesias. • Reducing the dose size of levodopa has been beneficial in reducing dyskinesias. The risk of off-time increases but can be compensated by increasing the frequency of levodopa dosing. • Discontinuing or reducing the dose of MAO-B inhibitors or COMT inhibitors can help control dyskinesias, however the risk of worsening off-time increases. • The addition of clozapine or quetiapine has shown to be beneficial in reducing peak dose dyskinesia. Clozapine's adverse effect of agranulocytosis limits its use. • Deep brain stimulation of the subthalamic nucleus allows the reduction of dopaminergic treatment. • Apomorphine given as a continuous subcutaneous infusion under direct medical supervision allows for the reduction of levodopa therapy and helps control dyskinesias.

Conclusions

The catechol-O-methyltransferase (COMT) inhibitor class is comprised of Comtan® (entacapone), and Tasmar® (tolcapone). These agents exert their therapeutic effect, by inhibiting the COMT enzyme and reducing the metabolism of levodopa, extending its plasma half-life and prolonging the action of each levodopa dose. They exhibit different pharmacokinetic characteristics which lead to their different dosing regimens. In clinical studies, both agents have proven effective for the treatment of motor fluctuations in

patients with Parkinson's disease. The current available guidelines do not specifically state which agents should be used first or which are preferred for the treatment of motor fluctuations. However, guidelines do recommend the COMT-inhibitors as a potential treatment option. Some also indicate that tolcapone should only be used as a second line agent in those patients who have tried and failed entacapone. This is due to the black box warning that is associated with tolcapone. The black box warning was added due to tolcapone having caused 3 deaths due to hepatic failure. This adverse event has not been reported in patients who have been treated with entacapone. Although both agents appear to be effective in treating the symptoms of patients with motor fluctuations, the potential for serious adverse events related to tolcapone potentially limits its use.

Recommendations

Based on the information presented in the review above and the safety concerns with tolcapone (Tasmar[®]), the following PDL changes are recommended.

Comtan[®] remains as a preferred agent on The Office of Vermont Health Access (OVHA) preferred drug list.

Tasmar[®] moves to PA required with the following criteria.

- The diagnosis or indication is Parkinson's disease.
AND
- The patient has had a documented side effect, allergy, or treatment failure with Comtan[®]

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